UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

IN RE: BENICAR (OLMESARTAN) PRODUCTS LIABILITY LITIGATION	**MDL No. 2606**
THIS DOCUMENT RELATES TO ALL CASES	**HON. ROBERT B. KUGLER** **CIVIL NO. 15-2606 (RBK)(JS)**

PLAINTIFFS' BRIEF IN SUPPORT OF DAUBERT MOTION TO PRECLUDE OPINIONS OF DEFENSE EXPERT KEITH WILSON, M.D.

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PRELIMINARY STATEMENT

Dr. Wilson contends that there is no causal association between Olmesartan and sprue-like enteropathy, despite overwhelming evidence to the contrary, including:

- **The FDA required a warning to be added to the Olmesartan drugs and issued a Drug Safety Communication to health care professionals and patients informing them that Olmesartan *can cause* intestinal problems known as sprue-like enteropathy.** Dr. Wilson's opinion directly contradicts the FDA's pharmacovigilance and medical review, which included a review and analysis of the medical literature, adverse event data including rechallenge data, the Mini-Sentinel and CMS Medicare Data Results, and review of potential mechanisms.

- **There is no peer-reviewed article that concludes there is not a causal association between Olmesartan and sprue-like enteropathy.**

- **The only randomized-controlled study relied on by the defense experts to deny a causal relationship is ROADMAP, which was not adequately powered to evaluate the causal relationship and was designed with no gastrointestinal endpoints.**

- **The defense experts admit that the medical literature is sufficient for clinicians to diagnose sprue-like enteropathy due to Olmesartan in a patient, and permanently withdraw Olmesartan.**

- **The type of clinical data sought by the defense experts does not exist because it would not be feasible to construct a randomized, controlled study of the question, and the medical literature establishes that it would be unethical to subject patients to controlled rechallenges.**

- **The defense experts have no clinical experience with sprue-like enteropathy.** In fact, Dr. Wilson learned of the existence of this syndrome only after being contacted by defense counsel.

- **None of the defense expert causation opinions are published or peer-reviewed.**

Dr. Keith Wilson, Defendants' gastroenterology expert, had zero knowledge of or experience concerning sprue like enteropathy, Olmesartan induced enteropathy, or Olmesartan associated enteropathy (interchangeably referred to as "SLE," "OIE," or "OAE"), until he was asked to be a defense expert in the Summer of 2016. Dr. Wilson reached the net opinion that

Olmesartan does not cause SLE in any patients, based solely on his review of literature, and is a conclusion not stated in any peer-reviewed publication. This outlier opinion is the product of multiple methodological flaws. The major systemic methodological flaw is Dr. Wilson's refusal to accord significance to any data from a study that was not controlled or randomized. As a result, he drastically discounted or rejected all positive evidence that was not generated by controlled, or randomized studies – including, for example, the many positive dechallenges and rechallenges documented in the literature and by the FDA, and in Daiichi's own files. Dr. Wilson also only paid lip service to applying an accepted scientific methodology, failed to consider significant relevant information, relied on inaccurate factual assumptions, and performed inadequate research by his own admission. The ultimate opinion yielded by this unscientific analysis, misleadingly cloaked in the terminology of science, is a superficial net opinion at best, essentially reduced to scoring a selected subset of articles based on how each study was performed. This enabled him to reach the predetermined conclusion that there are not enough "high level" studies proving causation to conclude that Olmesartan causes SLE – in part, based on the fact that nobody would perform a study sufficient to satisfy his personal standard by his own admission.

Dr. Wilson admits to the association between Olmesartan and SLE, admits that Olmesartan is the possible cause of the severe gastrointestinal conditions documented in key studies in the literature, and even admits that Olmesartan is the likely cause of the villous atrophy, severe diarrhea, weight loss, and hospitalizations described in certain published case reports. Despite these glaring admissions, his flawed methodology allows him to illogically deny general causation, in direct contradiction to the consensus in the literature as well as FDA's safety communication for healthcare providers to rely on, because the "Wilson test" requires controlled, randomized data to reach a conclusion of general causation. This methodology is unreliable, yielding a net opinion

based upon a personal standard at odds with science and the law. In addition to the inadmissibility of this net opinion under Daubert, the artificially narrow criteria designed to yield this opinion would be confusing and misleading to a jury since evidence generated by non-controlled, non-randomized studies is admissible and may be relied upon to make a finding of general causation. Thus, Dr. Wilson's refusal to fairly weigh this evidence in forming his opinion, without a satisfactory scientific solution, renders his opinion inadmissible and should be excluded under the *Daubert* standard.

STATEMENT OF FACTS

1. Dr. Wilson's Lack of Experience and Knowledge.

Dr. Wilson offers an isolated opinion that is not documented in the peer reviewed literature, having admitted that he cannot point to any article that concludes there is not causation in any patients. (Dr. Wilson Dep. Tr., 124:5-15; Exhibit 1 to the accompanying Certification of Adam M. Slater). Dr. Wilson's opinion disagreeing with the scientific consensus is not based on any directly relevant knowledge or experience, nor can it be, because he has no experience with "the evaluation or diagnosis of a potential olmesartan-related gastrointestinal illness." (Dr. Wilson Dep. Tr., 42:5-10). Dr. Wilson never even heard of OIE, or read any scientific literature about OIE, until defense counsel contacted him regarding this litigation eight or nine months ago, during the Summer of 2016. His entire understanding and knowledge of the clinical diagnosis and management of OIE is limited to what he has read in the literature as a defense expert. He has not published any articles regarding olmesartan, has not performed any research, and has had no involvement with the evaluation of any Olmesartan patients in a clinical setting. He has never even published any articles on celiac disease, the closely related enteropathic condition caused by

an immune reaction to gluten in genetically susceptible individuals. (Dr. Wilson Dep. Tr., 14:16-16:6, 22:13-22, 23:5-15, 24:19-24).[1]

Dr. Wilson's primary research interests are "inflammatory bowel disease…and gastric inflammation associated with Helicobacter pylori infection." (Dr. Wilson Report, not including CV, at 16; Slater Cert., Exhibit 2). Of note, although he accepts the causal connection between H pylori and gastric cancer, he admits that, "the specific mechanisms by which this pathogen induces carcinogenesis have not been fully elucidated." (Dr. Wilson Dep. Tr., 75:5-16). Dr. Wilson dedicates only about 10 hours per week to clinical responsibilities and the balance on administration and research. His clinical responsibilities are limited to performing endoscopies and some inpatient consultation at a VA hospital. This does not even involve the identification or diagnosis of celiac disease, or follow up on the biopsies he takes; rather, as Dr. Wilson puts it, "that is somebody else's job." (Dr. Wilson Dep. Tr., 17:7-21:19).

2. Dr. Wilson Parroted a Methodology Directed by Defense Counsel

Dr. Wilson agreed to provide his net opinion, "essentially after a review of the literature, giving your opinion about the strength of the literature in terms of the strength of the studies and whether from your review of the literature whether you think there is an association or a causal relationship shown by those studies described in the medical literature." (Dr. Wilson Dep. Tr., 42:11-43:2). Dr. Wilson stated in his report that in analyzing the literature he applied the Oxford standards of evidence based medicine (March 2009), the Bradford Hill criteria for assessment of

[1] The only two individual cases of OIE Dr. Wilson has ever evaluated are chart reviews on two of the bellwether discovery cases. (Dr. Wilson Dep. Tr., 127:16-128:14).

scientific evidence, and the Grading Recommendations Assessment, Development and Evaluation (GRADE) approach." (Wilson Report at 1; Slater Cert., Exhibit 2).[2]

The first time Dr. Wilson heard of the Bradford Hill criteria was when defense counsel told him, after he had reviewed the literature, that he needed to, "make reference to the Bradford Hill criteria," in his report. He then, "read a couple references that I listed there, and that's how I knew what the Bradford Hill criteria were." (Dr. Wilson Dep. Tr., 47:12-48:13). Dr. Wilson is so unfamiliar with this criteria that he could not tell whether it is necessary to find that all the criteria are satisfied to support a finding of causation.[3] He had never applied Bradford Hill criteria before writing his report, has read no "position paper that is agreed upon in the field as to exactly how many of the criteria need to be met," and did not study this question at all, rather he applied it based on his "own personal view of how to apply it." (Dr. Wilson Dep. Tr., 99:1-100:22). He said he was asked to address how the articles fit into the Bradford Hill criteria, but he was so unfamiliar with this standard, even at his deposition, that he could not even state whether the Bradford Hill criteria is an accepted scientific methodology. (Dr. Wilson Dep. Tr., 44:1-14).

Dr. Wilson also claimed to apply the Oxford Centre for Evidence Based Medicine, another standard he had never seen before being hired by the defense. He found this standard, through "Google and PubMed searching." (Dr. Wilson Dep. Tr., 50:18-22, 51:13-52:7). In fact, as it turns out, Dr. Wilson applied the outdated 2009 version of the Oxford standards, rather than the updated 2011 version.[4] In his report, Dr. Wilson cites to a version of the Oxford levels of evidence that was created in 2000. The Oxford Centre for Evidence Based Medicine website upon which these

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[2] Dr. Wilson has never cited the Oxford Centre for Evidence Based Medicine standards, the Bradford Hill criteria, nor the Grade approach in any paper he has ever published, nor has he taught any students the use of any of those three tools. (Dr. Wilson Dep. Tr., 295:8-296:7).

[3] It is well established that there is no requirement that all of the factors be met. In re Avandia Marketing, Sales Practices and Products Liability Litigation, 2011 WL 13576, No. 2007-MD-1871, at *3 (E.D. Pa. Jan. 4, 2011).

[4] Jeremy Howick et al., Explanation of the 2011 OCEBM Levels of Evidence, Centre For Evidence-Based Medicine, http://www.cebm.net/explanation-2011-ocebm-levels-evidence/. (Slater Certification, Exhibit 3).

outdated levels were posted was last updated in March 2009. However, Oxford noted on a different page in that same website that in 2009 the Levels were "over a decade old, and feedback over the years" led members to believe it was time to review them. Explanation of the 2011 OCEBM Levels of Evidence. CEBM. http://www.cebm.net/explanation-2011-ocebm-levels-evidence/ 2017. On this same website page, Oxford explained that:

> While they are simple and easy to use, early hierarchies that placed randomized trials categorically above observational studies were criticized for being simplistic. In some cases, observational studies find us the 'best' evidence. **For example, there is a growing recognition that observational studies – even case series and anecdotes can sometimes provide definitive evidence**.
>
> More recent evidence-ranking schemes such as GRADE avoid this common objection by allowing observational studies with dramatic effect to be upgraded, and trials may be 'downgraded' for quality and other reasons.

Id., emphasis added.

In 2011, the new Oxford levels of evidence were published. Changes included simplifying the number of levels from 10 to 5 and altering the types of evidence at each level. Notably, the column title Dr. Wilson pulls from in the 2000 Levels, entitled "Therapy/Prevention/Aetiology/Harm," (Dr. Wilson Report, page 2) no longer exists in the 2011 version. (See: Slater Cert., Exhibit 3). The 2011 list of evidence levels is notably different from the 2000 list. Whereas there is no mention of an "observational study with dramatic effect" in the 2000 levels, such study is given a Level 2 quality in the 2011 version. Id. Nowhere did Dr. Wilson explain or justify a decision to apply the outdated, superseded version of this standard.

Similarly, Dr. Wilson discovered the GRADE approach, which he had never utilized before, "while trying to find good articles that carefully described that nomenclature [referring to Bradford Hill criteria]." He admitted that he only "generally considered," and did not, "actually

apply the GRADE approach in terms of how you calculate the value of different criteria." (Dr. Wilson Dep. Tr., 275:22-277:4). The article Dr. Wilson cites on page 10 of his report in support of analyzing Bradford Hill with GRADE, states, "GRADE notes that randomization is only one of many relevant factors." Schunemann, et al. The GRADE approach and Bradford Hill's criteria for causation, J Epidemiol Community Health, 65:392-5, (2011). (Slater Cert., Exhibit 4). This article, relied on by Dr. Wilson, states that while GRADE places heightened value on an RCT, in some circumstances, "**observational studies may provide more relevant information than RCTs**." Schunemann at 392, emphasis added. The authors further state that "Bradford Hill suggests that a strong association supports causality. This criterion is directly considered in GRADE through upgrading. In the GRADE system, strong associations between an intervention or exposure and an outcome can lead to upgrading the quality of evidence, i.e., increases our confidence that the intervention causes a chance in the incidence of that outcome." See id. at 393. Yet, Dr. Wilson states, based on his personal test, that observational studies are inadequate to meet a Bradford Hill category because the evidence is "the weakest level of evidence." (Dr. Wilson Report at 11). This is in direct contradiction to the primary purpose of GRADE which was to move beyond the rigid grading system that puts RCT evidence on a pedestal without question.

3. Dr. Wilson's Failure to Consider Significant Literature and Information.

Dr. Wilson admitted that the correct approach in forming his opinion in this case was to "consider all relevant evidence on either side of the question." (Dr. Wilson Dep. Tr., 61:21-62:1). Yet, there are significant gaps in the information that Dr. Wilson considered. First, Dr. Wilson's search for relevant data was so perfunctory and limited, by his own admission, that it clearly demonstrates the lack of rigor, and lack of objective validity, to his analysis. Specifically, Dr. Wilson accessed the widely utilized, web based subscription service Up-To-Date, which is

accessed by clinicians, including himself, to aid them in evaluating and treating patients. (Dr. Wilson Dep. Tr., 28:5-32:14). Dr. Wilson relied on Up-To-Date, "to get a nice general overview of the workup of acute and chronic diarrhea," for the general discussion on page 13-14 of his report. (Dr. Wilson Dep. Tr., 31:12-32:3, 34:20-35:13). This was also reviewed by Plaintiffs' expert in gastroenterology, Dr. Benjamin Lebwohl, who pointed out that the site is peer-reviewed and identified and relied in part on the table in Up-To-Date listing Olmesartan as a cause of small intestinal villous atrophy. (Dr. Lebwohl Dep. Tr. 133:22-134:22; Slater Cert., Exhibit 5). In contrast, Dr. Wilson did not even notice that statement of causation. Dr. Wilson did not search for, "the causes of villous atrophy or sprue-like enteropathy [sic],", and admitted he did not "see anything on Up-To-Date indicating that olmesartan causes villous atrophy or enteropathy, anything of that nature." (Dr. Wilson Dep. Tr., 30:24-31:9). Dr. Wilson openly admitted the lack of rigor in his approach, and that he, "didn't find the fact that it lists causes of small intestinal villous atrophy other than celiac disease, and one of those listed is medications, for example, olmesartan." He admitted he was not thorough:

> Q: Did you attempt to be thorough in finding [regarding UpToDate] relevant information meaning relevant to the opinions you were going to give in this case?
>
> A: I don't think I would say thorough, no. I would say that I typed in there diarrhea evaluation or something like that and found what they said.

(Dr. Wilson Dep. Tr., 35:19-36:19). Dr. Wilson performed a similarly inadequate search of the textbook he claimed to have consulted, Sleisinger and Fordtran's "Gastrointestinal and Liver Disease," which he referred to as the bible of gastroenterology. He could not tell what edition he consulted, he only looked at the chapter on Celiac Disease, and did not, "look to see if there was

any discussion of olmesartan anywhere in the book," because "[i]t's kind of cumbersome trying to figure out how to use these online resources." (Dr. Wilson Dep. Tr., 36:20-39:6).

4. Dr. Wilson Ignored Celiac Disease.

Dr. Wilson claimed he reviewed a chapter in an influential textbook regarding celiac disease, yet he agreed that he did "not consider any analogies between celiac disease and olmesartan-associated enteropathy" in forming his opinion. (Dr. Wilson Dep. Tr., 104:4-14). This is a significant flaw in understanding causation here. For example, he states in his report that the lack of a "dose effect" between Olmesartan and intestinal harm argues against causation here, but he does not know whether the literature establishes there is a dose effect as between gluten and celiac disease. He did not realize the important overlap, "[s]o it did not occur to me to look at tens of thousands of papers about celiac disease and gluten....I'm not prepared to expound upon that detailed question." (Dr. Wilson Dep. Tr., 101:17-103:7).

5. Dr. Wilson Reviewed No Daiichi Documents.

Dr. Wilson was not provided any internal Daiichi documents or depositions of Daiichi witnesses, and does not know, "what Daiichi has done as to whether there is a causal relationship between olmesartan and olmesartan-associated enteropathy." He stated: "I have no information whatsoever about anything at the company." (Dr. Wilson Dep. Tr., 39:9-40:15). He could not even venture a guess as to whether review of the causality assessments by Daiichi in house physicians on adverse event reports, finding gastrointestinal syndromes to have a probable or definite relationship to Olmesartan in some patients, would have been useful: "I don't know what those reports would look like. So I don't know if they would be useful to me." (Dr. Wilson Dep. Tr., 46:13-47:9). Dr. Wilson did not see the adverse event reports that Daiichi had available, and did not see any of the Daiichi causality assessments, as he was not even, "curious as to whether Daiichi

was studying the question," of general causation. (Dr. Wilson Dep. Tr., 40:17-41:2). Since he was only, "assessing the medical literature and thinking about the science behind that," he was uninterested in internal documents because "they're not peer-reviewed. I don't know anything about how they're constructed or – or anything." (Dr. Wilson Dep. Tr., 208:4-17).

6. Dr. Wilson's Reliance on the ROADMAP Study.

Dr. Wilson relied on the ROADMAP study data as part of his methodology. (Dr. Wilson Dep. Tr., 203:1-7). Reliance on the incorrect factual assumption that the ROADMAP study was a scientifically valid study of gastrointestinal symptoms caused by Olmesartan undercuts the entire analysis. Dr. Wilson admitted that the primary endpoint was whether the use of Olmesartan was associated with a delay in developing kidney damage in diabetic patients (whereas non-diabetics use Olmesartan as well), not to evaluate gastrointestinal or any other side effects. (Dr. Wilson Dep. Tr., 226:7-18). Dr. Wilson did not perform power calculations to determine whether the ROADMAP study was sufficiently powered to look for sprue-like enteropathy or Olmesartan-associated enteropathy, did not draw any assumption as to whether the study was adequately powered to study that question, and has no opinion on whether the study is adequately powered. (Dr. Wilson Dep. Tr., 226:19-227:4, 233:7-13). Dr. Wilson does not even know whether Daiichi thinks the ROADMAP study was adequately powered to study the question. (Dr. Wilson Dep. Tr., 230:15-20). [5]

Dr. Wilson was also unaware of the causality assessments on patients in the Olmesartan arm of the ROADMAP study, including a patient who "developed gastroenteritis, vomiting, and diarrhea so severe that she was hospitalized. When she went off olmesartan, she got better. When

[5] Jeffrey Warmke, the 30(b)(6) representative regarding the ROADMAP study, admitted that the study was not designed or adequately powered to study gastrointestinal side effects caused by Olmesartan. (Jeffrey Warmke Dep. Tr., 111:5-11, 272:19-274:11, 279:9-282:16, 362:12-363:23; Slater Cert., Exhibit 6).

she went back on it, she got sick again." The causality assessment for the, "hospitalization because of gastroenteritis," was "probably related." (Jeffrey Warmke Dep. Tr., 327:21-334:24). Dr. Wilson admitted that if "a dechallenge and rechallenge were documented in a randomized controlled trial," that would be of significance to him and he would want "to look closely at and consider giving significant weight" to that data. However, he was never given that information by Daiichi, so he didn't consider it. (Dr. Wilson Dep. Tr., 188:10-189:15).

7. Dr. Wilson's Unscientific Rejection of the Basson epidemiological study

Dr. Wilson also was asked about the Basson epidemiological study of the French National Health Insurance database, which studied the rate of hospitalizations for malabsorption, comparing patients on Olmesartan to patients on other anti-hypertension medications. The study showed an, "adjusted rate ratio of hospitalization with a discharge diagnosis of intestinal malabsorption was 2.49 for olmesartan users…and 10.65…beyond 2 years of exposure," and concluded that, "Olmesartan is associated with an increased risk of hospitalization for intestinal malabsorption and celiac disease." (Slater Cert., Exhibit 7). Dr. Wilson so rigidly grasped to the conclusion he is advocating that he would not even agree that the data "would weigh in favor of a finding of causation," based on his perplexing analysis that "the data are weak because there's no individual chart review to validate anything. It's just an administrative database. There's no biopsies. There's no information about the patients."[6] He testified that he might give greater weight to the study if it had been a United States database, but admitted he has no scientific basis to discount the French data, and, "I would leave it to people that would dissect out this type of data on a daily basis who might be more familiar with the French versus the American administrative databases." (Dr.

[6] The criticism of studying administrative claims data is all the more striking since he relies in his report on the Padwal study of administrative claims data for far fewer patients taking Olmesartan, without criticizing the source of the data, and lack of chart reviews. He agreed the same criticisms would apply to Padwal, but distinguished the data based on Padwal's study of United States data, with no scientific basis. (Dr. Wilson Dep. Tr. 222:21-224:10).

Wilson Dep. Tr., 220:6-224:10). This decidedly unscientific approach to diminishing the value of a significant epidemiologic study of an administrative claims based database, showing a substantially elevated risk of being hospitalized for malabsorption while using Olmesartan, undercuts Dr. Wilson's overall methodology.

8. Dr. Wilson Ignored the FDA's Conclusion That Olmesartan Can Cause SLE.

Dr. Wilson did not, "factor in the FDA's evaluation," because "I don't consider that scientific evidence." (Dr. Wilson Dep. Tr., 77:3-11). He had not seen the FDA's Drug Safety Communication until it was shown to him at the deposition, and did not know it states that the FDA, "found clear evidence of an association between olmesartan and sprue-like enteropathy." (Dr. Wilson Dep. Tr., 78:8-79:12). The FDA confirmed that Olmesartan "can cause intestinal problems known as sprue-like enteropathy," in the Drug Safety Communication, which is designed to provide important safety information for patients and healthcare providers to rely on when making medical diagnoses. (Slater Cert., Exhibit 8). Dr. Wilson incorrectly denied that the FDA stated that Olmesartan "can cause" sprue like enteropathy, then he retreated to, "Frankly, I can't recall the exact language in the FDA product insert alteration because I haven't looked at that in over a month." (Dr. Wilson Dep. Tr., 59:3-61:19). As set forth, this information is in the Safety Announcement, not in the label, and **Dr. Wilson was not aware that in the Safety Announcement the FDA stated that it had identified 23 serious cases in the FAERS database presenting with diarrhea, significant weight loss and villous atrophy on biopsy where clinical improvement occurred after discontinuation of olmesartan and positive re-challenge was seen in 10 of the cases**. Even when shown this information, he refused to admit that it would

weigh in support of a finding of causation, because in his opinion, based on no true analysis or methodology, "It's not evidence." (Dr. Wilson Dep. Tr., 79:16-81:14).[7]

Compounding Dr. Wilson's ignorance of this important information, he was not even aware (as he failed to produce this in response to the deposition notice) that the website of Vanderbilt University, where he is employed, contains explicit reference to and discussion of the FDA Communication, including that Olmesartan "can cause intestinal problems known as sprue-like enteropathy." (Dr. Wilson Dep. Tr., 56:1-59:2). Dr. Wilson clung to his mantra, and rejected this statement as "that's just opinion and uncontrolled information....This is just pro forma regurgitation of something that was written by the FDA. It's not scientific evidence." (Dr. Wilson Dep. Tr., 62:4-22). He also acknowledged the clinical recommendation on the Vanderbilt website to tell patients prescribed Olmesartan to tell the physician, "if you have this clinical picture, severe, chronic diarrhea with substantial weight loss while taking an olmesartan-containing product, even if it takes months to years for symptoms to develop, you should come back to me as the physician and tell me this is happening while you're on Olmesartan." Then, he weakly tried to minimize this information as "just the FDA's recommendation that's pasted onto the Vanderbilt website," and "[t]his is a website that's sort of a repository of information about clinical research." (Dr. Wilson Dep. Tr., 64:22-65:21).

9. Dr. Wilson Applied an Unreasonably High Personal Standard.

Dr. Wilson applied an unreasonably high standard, personal to him, to determine causation (the "Wilson test"), setting the bar so high that relevant, admissible evidence would not be objectively factored into the analysis. Unless a study was a randomized, controlled study, it

[7] Dr. Wilson also did not know before his deposition that the FDA analysis showed Olmesartan users, "had a higher rate of celiac disease diagnoses – in claims and administrative data than users of other ARB's." He inexplicably dismissed this information, "It's not data like I'm looking at here." (Dr. Wilson Dep. Tr., 81:15-84:6).

received very little or no weight in Dr. Wilson's analysis, and in the absence of such a study demonstrating causation he would not give that opinion. (Dr. Wilson Dep. Tr., 163:23-165:19). The "Wilson test" was designed to yield a negative conclusion, since Dr. Wilson admitted it would not be feasible to conduct a controlled prospective study of gastrointestinal side effects of Olmesartan, it would be speculative to say that such a study could be constructed, and he has not "done that analysis or constructed any such study." He agreed that nobody would actually have an incentive to do that study and to spend that money." (Dr. Wilson Dep. Tr., 201:23-202:19, 233:16-234:21, 240:6-241:12). In other words, he says there is no general causation, since it has not been established by studies he admits have not been, and will not be, undertaken. Dr. Wilson also admitted that a drug can be deemed to cause an adverse drug reaction, "even if there's never been an RCT that studied that question," and that doctors establish practice patterns, based on clinical experience, even if the evidence is not Level I or II. (Dr. Wilson Dep. Tr., 52:8-23). Thus, his opinion is divorced from clinical and academic reality, and applies a narrower standard of admissibility than will apply at trial.

This approach led Dr. Wilson to fail to attach significance to important peer reviewed studies and case reports that strongly support causation. **For example, Dr. Wilson agreed that, "the evidence of dechallenges and rechallenges has to be looked at as an important component of the analysis," but only if "properly done," rejecting all dechallenges and rechallenges documented in case reports. Dr. Wilson's methodology led him to conclude that no documented dechallenges and rechallenges in the literature are scientifically valid.** (Dr. Wilson Dep. Tr. 241:19-242:5, 243:14-20). He stated, "**To me, a rechallenge has to be controlled." He will not rely on a documented rechallenge to determine causation, "unless it**

was done in a controlled way pursuant to a study protocol." (Dr. Wilson Dep. Tr., 184:14-186:1), emphasis added.

Dr. Wilson testified that even if the 22 patients reported by the Mayo Clinic in the initial publication in 2012 had the positive clinical response to withdrawal of Olmesartan described in the article, he still denies that this is "significant evidence of causation," because there was no study protocol, and the study was not randomized or controlled. (Dr. Wilson Dep. Tr., 166:9-167:24). This can be contrasted with the testimony of former Daiichi Vice President of CSPV Dr. Allen Feldman (never provided to or considered by Dr. Wilson), where Dr. Feldman admitted that the only plausible explanation for the syndrome suffered by the 22 patients in the Rubio-Tapia study (Slater Cert., Exhibit 9) was that it was caused by Olmesartan. (Allen Feldman Dep. Tr., 181:15-185:5; Slater Cert., Exhibit 10). Dr. Wilson ultimately had to admit that he was not offering, "an alternative diagnosis other than olmesartan-associated enteropathy as the cause of these patients – these 22 patients' clinical presentation." (Dr. Wilson Dep. Tr. 151:16-152:1). Similarly, in the Marthey study (Slater Cert., Exhibit 11), where 26 patients demonstrated clinical remission of the syndrome when taken off Olmesartan (and not on immunosuppression to improve the symptoms), Dr. Wilson admitted it would be a reasonable clinical judgment for a doctor to conclude, "the Olmesartan was causing the condition, so I don't want to put the patient back on the drug." Yet, on the other hand he would only agree that it was "possible" that the Olmesartan was the likely cause: "I mean, it's possible. **I don't know that I'm willing to say likely because, again, this is just sort of another case series**." (Dr. Wilson Dep. Tr., 247:10-249:21, emphasis added).[8]

[8] Dr. Wilson also admitted that factors he relied on to dispute causation in his report, including the lack of a dose effect, and the varied presentation of the syndrome (like celiac, where "the presentations can be highly variable"), do not disprove causation. (Dr. Wilson Dep. Tr., 103:8-104:3, 145:17-146:21).

10. Dr. Wilson's Admissions of Association and Causation.

Dr. Wilson agreed that there is a spectrum of association, from unlikely to be causal, to causal associations, where the drug causes the condition. (Dr. Wilson Dep. Tr., 109:9-17). He agreed that there are "case series suggesting an association," and wrote in his report that this is an association, albeit not causal. (Dr. Wilson Dep. Tr., 109:19-110:6, 147:18-22).

Dr. Wilson was asked about the patients discussed in various peer-reviewed articles discussing OIE. On the Rubio-Tapia study, he admitted that Olmesartan was "a potential cause" of the patients' villous atrophy, and could not state an alternative cause to a reasonable degree of medical certainty. (Dr. Wilson Dep. Tr., 172:13-20, 174:22-175:5). Dr. Wilson addressed a published case report titled: Kulai, et al., Duodenal Villous Atrophy in a TTG-Negative Patient Taking Olmesartan: A Case Report and Review of the Literature, Canadian Journal of Gastroenterology and Hepatology, Volume 2016 (Slater Cert., Exhibit 12), in which there was a dechallenge, and, "significant improvement in the histopathology at 14 weeks, the resolution of the clinical symptoms of non-bloody diarrhea, vomiting, and a 20-pound weight loss after the patient stopped taking the olmesartan," and admitted that Olmesartan is, "a potential cause," of the syndrome. He then agreed Olmesartan is, "the most likely cause," based on the data provided. (Dr. Wilson Dep. Tr., 250:6-260:14). Dr. Wilson addressed another published case report titled: Gallivan and Brown, Olmesartan induced enterocolitis, Pathology (2014), 46(4) (Slater Cert., Exhibit 13), regarding a 78 year old female patient, which provides detailed clinical information on the patient, including severe watery diarrhea, dehydration and acute renal failure, three hospital admissions, a positive dechallenge, positive rechallenge, and another positive dechallenge, and admitted that the most likely cause of her syndrome was Olmesartan. (Dr. Wilson Dep. Tr., 265:18-271:13).

11. Dr. Wilson Admits the Literature Supports A Clinical Assumption of Causation.

Dr. Wilson admitted that the literature fully supports the prevailing understanding in the clinical community of specialists who treat OIE, that Olmesartan causes sprue-like enteropathy. Dr. Wilson specifically agreed that, "**Based on the literature that exists now**," it would be reasonable for a doctor to stop a patient from using Olmesartan based on presentation of severe diarrhea, dehydration, and weight loss, and not restart the drug if the symptoms improved off the drug. His response was telling: "I think that's reasonable, but I don't think that most doctors are aware of **this syndrome**." (Dr. Wilson Dep. Tr., 274:13-275:6, emphasis added). This is a glaring admission that the literature establishes causation to the level that doctors can rely on and treat patients, and that, in his words, this is a "syndrome."

I.

THE DAUBERT STANDARD

The admissibility of expert testimony is determined in Federal Court pursuant to Federal Rule of Evidence 702. The party offering the proposed expert testimony bears the burden of establishing the admissibility of the testimony by a preponderance of the evidence. Padillas v. Stork-Gamco, Inc., 186 F.3d 412, 417-18 (3d Cir. 1999). This Court has discussed the standard:

> A reliable opinion is based on the 'methods and procedures of science rather than on 'subjective belief or unsupported speculation; the expert must have 'good grounds' for his or her belief.... The focus of the reliability inquiry is on the expert's principles and methodology, not on his conclusions.... In determining reliability, a court may look to several non-exhaustive factors, including:
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> > (1) whether a method consists of a testable hypothesis; (2) whether the method has been subject to peer review; (3) the known or potential rate of error; (4) the existence and maintenance of standards controlling the technique's operation; (5) whether the method is generally accepted; (6) the relationship of the technique to methods which have been established to be reliable; (7) the qualifications of the expert witness testifying based on the methodology; and (8) the non judicial uses to which the method has been put.

Geiss v. Target Corp., 2013 WL 4675377 at *4-5 (D.N.J. 2013), citing Pineda v. Ford Motor Co., 520 F.3d 237, 243 (3d Cir. 2008) (other citations omitted). An "expert's opinions must be based on the methods and procedures of science, rather than on subjective belief or unsupported speculation." In re Paoli Railroad Yard PCB Litigation, 35 F.3d 717, 742 (3d Cir. 1994) (citations and internal quotations omitted). Thus, "the expert must have 'good grounds' for his or her belief." Id., citing Daubert, 509 U.S. at 590, 113 S.Ct. 2786. These good grounds must support each step of the analysis and "any step that renders the analysis unreliable under

the Daubert factors renders the expert's testimony inadmissible." Id. at 745. The Court will also consider how and when the methodology is used outside of litigation. In re Paoli, 35 F.3d at 742 (discussing reliability factors under Daubert and Third Circuit case law).

II.

DR. WILSON'S OPINION DENYING GENERAL CAUSATION SHOULD BE PRECLUDED PURSUANT TO *DAUBERT*

Dr. Wilson should not be permitted to advance his opinion that Olmesartan does not cause OIE in any users of the drug because the opinion is based on an analysis that is opposed to and inconsistent with the methodology that has yielded the scientific consensus established in the scientifically validated studies and data found in the peer-reviewed medical literature. Dr. Wilson's methodology was wholly personal to the witness and followed no recognized standard, yielding a new opinion. In truth he ignored a great deal of relevant, admissible scientific information without a satisfactory basis, and simply backfilled criticisms onto the peer-reviewed data, to get to the predetermined conclusion that there is no general causation because there is no controlled, randomized study proving causation – a study he admits he cannot construct and nobody would perform.

Dr. Wilson had no knowledge or experience regarding OIE until he was hired as a defense expert, and his entire analysis was constructed for litigation purposes only. This lack of knowledge and experience, and analysis divorced from what is occurring in the medical community, should result in greater scrutiny of the method actually applied by the expert. Although the Court's inquiry into reliability is focused primarily "on principles and methodology, not on the conclusions that they generate," the Supreme Court has recognized that "conclusions and methodology are not entirely distinct from one another." General Elec. Co. v. Joiner, 522 U.S. 136, 146, 118 S.Ct. 512, 139 L.Ed.2d 508 (1997). The Court should conduct at least a limited review of an expert's

conclusions, "in order to determine whether they could reliably flow from the facts known to the expert and the methodology used." Heller v. Shaw Indus., Inc., 167 F.3d 146, 152 (3d Cir.1999); see also In re TMI Litig., 193 F.3d 613, 682 (3d Cir.1999) (finding that the District Court did not abuse its discretion in excluding an expert's conclusion based upon a logical analysis of the expert's testimony).

In essence, Dr. Wilson applied a personal standard that willfully ignores or unreasonably downgrades to insignificance the significant evidence supporting causation, leading to his outlier net opinion. In granting a motion to preclude an expert under *Daubert*, this Court has observed:

> However, courts also need not admit mere conclusions or opinion evidence that is connected to existing data only by the *ipse dixit* of the expert. A court may conclude that there is simply too great an analytical gap between the data and the opinion proffered.... Mere assumptions, without causal evidence or methodological analysis may be inadmissible....Conclusions based only on the expert's experience, and testimony founded on methods that are not generally accepted or lack testable hypotheses may also fail to surmount the Daubert standard. Furthermore, conclusions based on analogies that are too dissimilar to the subject of the testimony may also merit exclusion.

Player v. Motiva Enterprises LLC, 2006 WL 166452 at *6-7 (D.N.J. January 20, 2006) (citations omitted). In Player, this Court found the expert failed to satisfy the reliability requirement, as the expert failed to consider important facts without satisfactory explanation, relied on, "a highly misleading analogy," and relied on a scientifically unsound survey. Id. at *8.

A. Dr. Wilson's Personal Test Is Not A Sound Methodology

Dr. Wilson's methodology must be closely scrutinized. In essence, Dr. Wilson was informed of the existence of OIE and given articles to read. He reviewed the articles and did a paucity of admittedly incomplete research on his own, then reported back to defense counsel, who told him to pay lip service to applying the Bradford Hill criteria so that he could claim to have

applied a scientifically valid method. Courts recognize the Bradford Hill factors as, "nine factors widely used in the scientific community to assess general causation." Glynn v. Merck Sharp & Dohme Corp., 2013 WL 1558690 at *3 (D.N.J. April 10, 2013) (citation omitted). These factors are used to establish general causation, which is defined as "when an observed association between a chemical and a disease is causal," and it is well established that "[o]ne or more of the factors may be absent even where a causal relationship exists and …no factor is a sine qua non of causation." Id. (citation omitted). These principles certainly validate an expert who applies the Bradford Hill criteria, but here Dr. Wilson could only speculate at his deposition how this method is applied, and could not even tell whether it is scientifically accepted.

Dr. Wilson had never heard of Bradford Hill, and then claimed to also incorporate the Oxford Centre's outdated 2009 hierarchy of evidence, and the GRADE approach, which he found on his own cursory research, but admitted in his deposition he considered, but did not actually apply. Therefore, he constructed his own confused method of analysis that incorporated more than Bradford Hill, and could not be replicated by other experts. This is not reliable. On top of this methodological chaos, he neglected to factor in important evidence of causation, because he either did not know it existed until he was deposed (i.e. FDA data and conclusions, Daiichi data and findings), or because he decided the study lacked a protocol, was not randomized, and/or was not controlled, and his explanations were decidedly subjective and unscientific (*see* rejection of Basson study because the data was French; rejection of all dechallenges and rechallenges documented in the literature). On the other hand, he selectively relied on a handful of studies, including the ROADMAP which was designed to study a different question, on a diabetic population, and underpowered to answer the question of causation. He admitted the association is established, and recognized the likelihood of causation based on the data reported in significant

peer reviewed studies, and well documented case reports, but then devalued this data to the point of insignificance based on his subjective, ultra-selective, unscientific criteria, designed to make it impossible to establish general causation in this case. This methodology, designed to justify an opinion not found in any peer reviewed article, is unreliable.

Dr. Wilson also utterly failed to scientifically account for contrary evidence. In re Zoloft Products Liability Litigation, 26 F.Supp.3d 449, 460-61 (E.D.Pa. 2016) (citing In re Rezulin Products Liability Litigation, 369 F.Supp.2d 398, 425 (S.D.N.Y. 2005)) (finding that "if the relevant scientific literature contains evidence tending to refute the expert's theory and the expert does not acknowledge or account for that evidence, the expert's opinion is unreliable."). For example, the rejection of the Basson data, in part because it was derived from the French national health database, and conclusory rejection of all of the FDA's data and findings, are fundamental flaws. The fact that his conclusions are drawn from a self-selected subset of data, "not the totality of the epidemiological evidence, further underscores his problematic methodology." Id. at 461-62.

Dr. Wilson's refusal to factor in the dechallenge and rechallenge evidence, since not from controlled studies, is particularly egregious. The scientific literature recognizes the central diagnostic importance of this medical evidence. In re Zoloft Products Liability Litigation, 176 F.Supp. 3d 483 at 460-61 (E.D. Pa 2016) (valuing adverse event reports that included "dechallenge and rechallenge events"); Rolland v. Smithkline Beckman Corp., 1990 U.S. Dist. LEXIS 6252, at *109-110 (E.D. Pa. May 22, 1990) (finding that "[a] positive rechallenge, at least in the absence of clear evidence to the contrary, is generally considered as the strongest and almost conclusive evidence that the drug is the cause of the adverse reaction"); McCarrell v. Hoffman La Roche, Inc., 2009 N.J. Super. Unpub. LEXIS 558, at *28 (Super. Ct. App. Div. Mar. 12, 2009) (stating

"[w]e also find significant that the case reports here included dechallenge and rechallenge reports. Dechallenge and rechallenge reports are included in, or are a type of, a case report. Such reports, although they surely have limitations, have been considered valuable in ascertaining causation because they measure a patient's reaction to a drug").

Though admitting that the likely cause of the syndrome described in Rubio-Tapia and Marthey is OIE, based in large part on the documented dechallenges, and unable to offer an alternative cause, he refused to weigh these studies as establishing general causation because they were not controlled, randomized, pursuant to a protocol. There is no recognized scientific standard for causation that requires such a prohibitive level of evidence, particularly in a situation like that here, where nobody (including Daiichi) has performed prospective research on this question, and the expert admits he could not even construct a study protocol to do so.

The refusal to consider scientific evidence that does not involve a randomized controlled trial is not supported in law. Nothing requires the evidence to take the form of, or to be comprised, even in part, of epidemiological evidence. See e.g., In re Tylenol (Acetominophen) Mktg., 2016 U.S. Dist. LEXIS 97367, at *19-20, 22 (E.D. Pa. July 26, 2016) (stating that "[w]hile epidemiological studies can be valuable evidence of causation, they are not a pre-requisite for products liability causation expert testimony in this Circuit.") (further stating that "in this case especially, epidemiological studies and/or statistically significant clinical evidence would be difficult to obtain"); In re Asbestos Litig., 911 A.2d 1176 (Del. Super. Ct. 2006) (finding that Plaintiffs need not support their general causation case with epidemiological evidence as a matter of law."); Yates v. Ford Motor Co., 2015 U.S. Dist. LEXIS 70476, at *9 (E.D. N.C. May 29, 2015) (stating that there is "nothing unreliable, in general, about consulting case reports" when determining what was known regarding asbestos and defendants' brake products).

Moreover, he never explains, in a scientifically adequate way, the illogical inconsistency between his admission that the patients in various peer reviewed studies documenting dechallenges and rechallenges likely suffered from OIE, while still denying general causation. If patients reported on in the peer reviewed literature likely suffered from OIE, that means some patients do suffer this syndrome due to use of Olmesartan. Thus there is general causation by definition Exclusion of this important evidence based on application of an untestable standard (since no controlled, prospective, randomized study of this question could be constructed) is unscientific.

Dr. Wilson's reliance on the ROADMAP study presents additional bases to exclude the opinion. First, the study is underpowered to answer the question he was asked to answer, yet he gives importance to and relies on the data for that purpose. Second, since the existence of ROADMAP patients with clinical symptoms of OAE, including one with confirmed dechallenge and rechallenge, was not disclosed to the expert, and the expert admits this information he has never seen would be of significance, his opinion should be rejected.

CONCLUSION

For the foregoing reasons, Dr. Wilson should be precluded from offering his opinion denying general causation.

Respectfully,

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